Incidental Renal Artery Stenosis Is an Independent Predictor of Mortality in Patients with Peripheral Vascular Disease

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In patients with peripheral vascular disease (PVD), mortality is high and renal artery stenosis (RAS) is a frequent incidental finding. RAS carries a high risk for mortality, but whether incidentally discovered RAS is a risk factor for mortality is unknown. The prognostic impact of incidental RAS for mortality was studied in 550 consecutive patients who underwent intra-arterial digital subtraction angiography for PVD in a single center between 1997 and 2000. In 491 patients (336 men, 155 women; mean follow-up 3.8 ± 1.9 yr), the renal arteries were visualized and follow-up data were available. RAS (diameter reduction >50%) was present in 26% of the patients. Mortality in the RAS group was 59 versus 28% in the non-RAS group (odds ratio 3.8; 95% confidence interval 2.5 to 5.7; P < 0.0001). Diabetes, previous myocardial infarction, history of PVD, stroke, and hypertension were more frequent in the RAS group; age was higher and GFR was lower in the RAS group. Therefore, RAS was associated with elevated mortality and increased prevalence of cardiovascular risk factors. Cox regression analysis showed that RAS was an independent predictor for mortality (P = 0.005), along with age, diabetes, smoking, previous myocardial infarction, history of PVD, and stroke. In patients who were evaluated for PVD by digital subtraction angiography, mortality was high. Incidental RAS was a frequent finding and an independent predictor for mortality. Whether RAS is a marker for, or, alternatively, a mediator of the poor prognosis and whether prognosis can be improved by specific intervention should be the subject of future prospective studies.


Materials and Methods

We reviewed a cohort of 550 consecutive patients who had clinically confirmed PVD by noninvasive examinations (ankle-brachial index or duplex Doppler of the lower extremities) and underwent angiography with the intention of surgical or radiologic intervention from January 1997 to December 2000 in a single center, as judged by the vascular surgeons. Patients in whom the angiogram did not allow proper assessment of the renal arteries were excluded from the analysis. A single reviewer, who was blinded to patients’ diagnoses and indications for the procedure, evaluated the angiograms for RAS. A diameter reduction of >50% was considered diagnostic for presence of RAS; severe stenosis was considered to be present when the stenosis exceeded 75% (10). Clinical data were obtained from patient records, and mortality data were obtained from the hospital information system.

Definitions

Hypertension was defined according to the 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension (16,17), prescription of antihypertensive medications, or a clinical history of hypertension. A patient was classified as having diabetes when there was a clinical history of diabetes or when the patient was taking insulin or oral antidiabetic agents. We used the abbreviated Modification of Diet in Renal Disease

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ISSN: 1046-6673/1707-2069
equation advocated in the Kidney Disease Outcomes Quality Initiative guidelines (18) to estimate GFR. These data are presented in this article. In addition, we estimated GFR by the quadratic equation proposed by Rule et al. (19), because this equation is assumed to provide a better estimate of renal function in patients in whom renal function is normal or only mildly impaired. All analyses also were performed using estimated GFR by the latter equation; this did not alter the results (data not shown).

**Baseline Characteristics**

Eight clinical variables were recorded at baseline (i.e., time of angiography): Serum creatinine before angiography, history of myocardial infarction, history of stroke, diabetes (present or absent), smoking history (ever/stopped or never), history of previous PVD (i.e., previous treatment either conservative or not otherwise specified), history of hypertension, and current BP at time of angiography.

**Statistical Analyses**

Comparisons between groups (RAS versus non-RAS) on baseline variables were done using χ² test. Survival was assessed by Kaplan-Meier curves, and to test for independent predictors of mortality, we performed multivariate analysis using single-step Cox regression analysis. The renal function was classified according to the cutoffs recommended in the Kidney Disease Outcomes Quality Initiative criteria (18) for defining moderate (GFR 30 to 60 ml/min per 1.73 m²) and severe (GFR <30 ml/min per 1.73 m²) renal function impairment. All statistical analyses were performed in SPSS 12.0 for Windows. Statistical significance was defined as P < 0.05.

**Results**

From January 1997 to December 2000, 550 consecutive angiograms were performed in patients with confirmed PVD. The renal arteries could be assessed in their entirety for RAS (diagrams were performed in patients with confirmed PVD). The reasons for incomplete visualization of the renal arteries were technical. Of the 499 assessable patients, eight could not be included because of incomplete clinical data. Atherosclerotic RAS was present in 129 (26%) of the 491 patients; of these patients, 35 (27%) had a luminal RAS of >75%, and 74 (57%) had a bilateral RAS.

Baseline characteristics of the population are presented in Table 1 and were divided according to the presence or absence of RAS. Patients with RAS were significantly older and their mortality was significantly higher than in patients without RAS (59 and 28%, respectively; P < 0.0001). In patients with RAS, the prevalence of several cardiovascular risk factors (hypertension, diabetes, previous history of PVD, myocardial infarction, and stroke) was higher than in patients without RAS, but the proportion of smokers, remarkably, was lower in the group with RAS. As shown by the Kaplan-Meier survival curves in Figure 1, the estimated 5-yr survival probability was 37% for patients with RAS as compared with 72% for patients without RAS (odds ratio 3.76). Patients with moderate and severe renal function impairment were overrepresented among the patients with RAS as compared with the group without RAS (Table 2). Among patients with RAS ≥75%, the majority had moderate or severe renal function impairment, whereas this amounted to approximately one third of the patients with RAS <75% (Table 2). Mean GFR was 67.2 ± 25.4 ml/min for RAS <75% versus 54.8 ± 26.4 ml/min for RAS ≥75% (P = 0.016). Therefore, RAS and its severity are associated with the severity of renal function impairment. The association of renal function and unilateral RAS versus bilateral RAS was NS (data not shown).

The crude mortality rates by absence or presence and severity of RAS is given in Table 3, showing significant effects of presence and severity of RAS on mortality, both for the population as a whole and after stratification of GFR in each of the various strata of GFR, i.e., normal to mildly impaired renal function (GFR >60 ml/min), moderately impaired renal function (GFR 30 to 60 ml/min), and severely impaired renal function (GFR <30 ml/min). Mortality was particularly high in patients with moderate and severe renal function impairment. Time-dependent survival by presence or absence of RAS and by stratum of renal function is shown as Kaplan-Meier curves in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No RAS (n = 362)</th>
<th>RAS (n = 129)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr; mean ± SD)</td>
<td>65 ± 11</td>
<td>72 ± 10</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Male gender (% [n])</td>
<td>70.4 (255)</td>
<td>81 (62.8)</td>
<td>0.108</td>
<td></td>
</tr>
<tr>
<td>Mortality (% [n])</td>
<td>27.6 (100)</td>
<td>58.9 (76)</td>
<td>&lt;0.0001</td>
<td>3.76 (2.47 to 5.71)</td>
</tr>
<tr>
<td>Systolic BP (mmHg; mean ± SD)</td>
<td>152 ± 26</td>
<td>153 ± 28</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg; mean ± SD)</td>
<td>83 ± 13</td>
<td>83 ± 16</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>History of hypertension (% [n])</td>
<td>53.9 (195)</td>
<td>71.3 (92)</td>
<td>0.001</td>
<td>2.10 (1.36 to 3.25)</td>
</tr>
<tr>
<td>History of diabetes (% [n])</td>
<td>27.1 (98)</td>
<td>39.5 (51)</td>
<td>0.01</td>
<td>1.74 (1.14 to 2.66)</td>
</tr>
<tr>
<td>History of myocardial infarction (% [n])</td>
<td>19.6 (71)</td>
<td>32.6 (42)</td>
<td>0.003</td>
<td>1.98 (1.26 to 3.11)</td>
</tr>
<tr>
<td>History of stroke (% [n])</td>
<td>14.9 (54)</td>
<td>22.5 (29)</td>
<td>0.049</td>
<td>1.66 (0.99 to 2.74)</td>
</tr>
<tr>
<td>History of smoking (% [n])</td>
<td>63.3 (229)</td>
<td>49.6 (64)</td>
<td>0.003</td>
<td>0.54 (0.36 to 0.81)</td>
</tr>
<tr>
<td>History of previous PVD (% [n])</td>
<td>30.7 (111)</td>
<td>45.0 (58)</td>
<td>0.003</td>
<td>1.85 (1.22 to 2.79)</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m²; mean ± SD)</td>
<td>79.7 ± 25.0</td>
<td>63.8 ± 26.2</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; PVD, peripheral vascular disease; RAS, renal artery stenosis.
Figure 2. It shows that RAS and GFR < 60 ml/min both were associated with worse survival, with the poorest survival in patients with both RAS and GFR < 60 ml/min (overall log rank test \( \chi^2 P < 0.0001 \); group 1 versus group 2 \( P = 0.0025 \), relative risk [RR] 1.89, 95% confidence interval [CI] 1.31 to 3.49; group 3 versus group 1 \( P < 0.0001 \), RR 2.44, 95% CI 1.92 to 5.41; group 4 versus group 1 \( P < 0.0001 \), RR 4.61, 95% CI 2.92 to 22.8).

The independent contribution of the various risk factors for mortality was assessed by Cox regression analysis, as shown in Table 4. It shows first the crude model, in which the widely known cardiovascular risk factors age, diabetes, history of previous PVD, smoking, previous myocardial infarction, and previous stroke were independent predictors for mortality. The contribution of stratum of renal function reached significance only for GFR < 30 ml/min (\( P = 0.047 \)). When the model was adjusted for presence of RAS, the contribution of class of renal function was attenuated, whereas RAS was an independent predictor for mortality (\( P = 0.005 \)).

**Discussion**

Our data confirm that incidental RAS is a frequent finding in patients who are evaluated for PVD by DSA. The main finding of our study is that we demonstrated, for the first time, that RAS is an independent predictor of mortality in this population. Moreover, we found that incidental RAS was closely associated with the level of renal function. Remarkably, the prognostic impact of incidental RAS was true both in patients with normal or mild renal function impairment and in patients with moderate to severe renal insufficiency.

The prevalence of incidental atherosclerotic RAS in our population was 26%, which is well within the range observed in other studies on PVD, in which prevalences ranged from 5 to 40% (6–8). Prevalence obviously can be confounded by the definition used; our definition of RAS (a 50% reduction in renal artery lumen) is in line with similar studies on survival in coronary artery disease (9,10), and our cutoff for severe stenosis (\( \geq 75\% \) luminal narrowing) is in accordance with the study described by Conlon et al. (10).

In patients with PVD, mortality is high. McKenna et al. (1) found a 5-yr survival of 44% in patients with PVD (as demonstrated by an ankle-brachial index of < 0.4) versus an 85% survival in patients without vascular disease. Criqui et al. (2) reported a 5-yr survival of 70% in patients with symptomatic PVD versus 90% in normal individuals. When renal insufficiency was present concomitantly, mortality was even higher, with a 1-yr survival rate of 56% for patients with a GFR < 30 ml/min per 1.73 m\(^2\) compared with 83% for patients with a GFR > 60 ml/min per 1.73 m\(^2\) (5). The overall mortality in our patients is in line with these studies, but our data also show that the subgroup with RAS has a prognosis that is considerably worse. Also, in patients with symptomatic RAS, mortality is

| Table 2. Distribution of baseline GFR according to the presence or absence of RAS and the severity of RAS |
|-------------------------------------------------|--------|--------|--------|--------|
| GFR > 60 ml/min | No RAS \((n = 362)\) & 78.7% (285) & 55.8% (72) & \( <0.0001 \) & RAS < 75% \((n = 94)\) & 63.8% (60) & 34.3% (12) & 0.003 & RAS \( \geq 75\% \) \((n = 35)\) & 6.4% (6) & 14.3% (5) & 0.153 |
| GFR 30 to 60 ml/min | No RAS \((n = 129)\) & 20.7% (75) & 35.7% (46) & 0.001 & RAS < 75% \((n = 28)\) & 29.8% (28) & 51.4% (18) & 0.023 & RAS \( \geq 75\% \) \((n = 18)\) & 29.8% (28) & 51.4% (18) & 0.023 |
| GFR < 30 ml/min | No RAS \((n = 35)\) & 0.6% (2) & 8.5% (11) & \( <0.0001 \) & RAS < 75% \((n = 12)\) & 6.4% (6) & 14.3% (5) & 0.153 |

\( ^a \)No RAS versus RAS.

\( ^b \)RAS < 75% versus RAS \( \geq 75\% \).

| Table 3. Overall mortality and distribution of GFR according to presence or absence of RAS and severity of RAS |
|-------------------------------------------------|--------|--------|--------|--------|
| All patients | No RAS \((n = 362)\) & 27.6% (100/362) & 54.3% (51/94) & 71.4% (25/35) & 0.0001 |
| GFR > 60 ml/min | No RAS \((n = 129)\) & 23.9% (68/285) & 45% (27/60) & 58.3% (7/12) & 0.0001 |
| GFR 30 to 60 ml/min | No RAS \((n = 35)\) & 41.3% (31/75) & 64.3% (18/28) & 72.2% (13/18) & 0.017 |
| GFR < 30 ml/min | No RAS \((n = 35)\) & 50% (1/2) & 100% (6/6) & 100% (5/5) & 0.047 |
High levels of angiotensin II are associated with left ventricular hypertrophy, endothelial dysfunction, and target organ damage (23). This pathway could explain, at least partially, the increased mortality in symptomatic atherosclerotic RAS. If this would be the case, then it would be logical to assume that pharmacologic blockade of the renin-angiotensin aldosterone system might have the potential to ameliorate the poor prognosis, but obviously this assumption would need empirical substantiation.

Second, our data suggest that incidentally found RAS can serve as a marker of a poor prognosis. When RAS is present, it is a strong marker of extended cardiovascular disease as suggested by the well-established clinical predictors of incidental RAS. Therefore, it could well be a marker of more extended coronary or cerebrovascular disease and thus related to increased mortality. In this perspective, it has been shown that in patients who undergo diagnostic cardiac catheterization simultaneously with an aortography, incidental RAS was an independent risk factor for mortality (9,10). Moreover, the severity of RAS was related to mortality. In our study, however, no appropriate characterization of coronary or cerebrovascular disease was available, because the patients all were referred to the hospital by the general practitioner because of suspicion of PVD and were evaluated and treated by the vascular surgeon only. Therefore, a possible relationship between RAS and its severity and coronary artery disease cannot be made for our population.

As anticipated, several well-established clinical predictors of incidental RAS, namely older age (24–26), hypertension (24,25,27,28), impaired renal function (24,28), a history of coronary artery disease (9,10,24,26), and diabetes (25,27,28) were more prevalent in our group with RAS, with the exception, however, of a history of smoking (25,27). This seeming discrepancy may be due to bias by indication, because the patients with RAS were older and had more symptomatic comorbidity and therefore were more likely to have received previous advice to stop smoking. Whereas the difference in prevalence of risk factors may have contributed to the overall difference in mortality, the Cox regression analysis demonstrated the independent contribution of RAS.

The clinical implications of incidentally discovered RAS so far are uncertain. Studies on its natural history (6,15,29,30) reported that progression to end-stage renal failure is rare (6,7). From the perspective of preservation of renal function, therefore, revascularization is not recommended for patients with incidentally discovered RAS (6,7). It may be worthwhile to refer these patients to the internist or cardiologist for a thorough screening for cardiovascular disease and for aggressive cardiovascular preventive therapy. It is known that aggressive treatment of hypertension and strict regulation of diabetes improve cardiovascular morbidity and mortality (31–33) and that an intensive lipid-lowering statin regimen can improve prognosis in high-risk populations (34).

Some limitations of our study should be considered. Because this was a retrospective post hoc analysis, we were not able to evaluate all the renal arteries in the patients. In addition, all but eight patients were included in the follow-up. Unfortunately, the specific number of deaths as a result of cardiovascular increased, but the reported mortality rates are lower than in our patients with RAS. Isles et al. (14) reported a 5-yr survival probability of 83% for patients with renovascular hypertension, and Wollenweber et al. (13) found a 5-yr survival of 67% for patients with atherosclerotic renovascular disease versus 90% for the general population. A more recent study by Wright et al. (15) showed a mortality rate of 35.7% for patients with atherosclerotic renovascular disease using a mean follow-up of 27.7 mo. Whereas a direct comparison is not warranted, our data nevertheless suggest that incidental RAS in patients with PVD carries a particularly poor prognosis, especially in patients with moderate to severe renal failure (of whatever cause).

What would be the implications of our findings? First, our study is the first to allow for mutual association among RAS, renal function impairment, and mortality in patients with PVD. These data may provide a potential pathogenic link between the association of PVD and renal insufficiency (20) and the association between renal function impairment and increased mortality in patients with PVD as described by O’Hare et al. (5), respectively. Our data suggest that a considerable proportion of the presence of renal function impairment in PVD can be ascribed to the presence of RAS but do not allow a conclusive dissection as to which of the two is the main causal factor for mortality. It is remarkable in this respect that adjustment for RAS attenuated the impact of renal function in the multivariate model, but considering their close association, it presumably would be overly artificial to attempt to disentangle their respective impact, so whether RAS is an independent causal factor remains hypothetical. In principle, RAS in itself can exert deleterious pathophysiologic effects by excess production of angiotensin II (21), which is a potent vasoconstrictor that has been implicated in the activation of cell proliferation systems (22). High levels of angiotensin II are associated with left ventricular hypertrophy, endothelial dysfunction, and target organ damage (23). This pathway could explain, at least partially, the increased mortality in symptomatic atherosclerotic RAS. If this would be the case, then it would be logical to assume that pharmacologic blockade of the renin-angiotensin aldosterone system might have the potential to ameliorate the poor prognosis, but obviously this assumption would need empirical substantiation.

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problems is not known because cause of death was not specified in our patient data and our hospital information system was not linked to a national registry for death registration. All the angiograms were performed in the same center; as a result, it may influence the generalizability of our findings. However, all angiograms were analyzed by the same radiologist, who was blinded to patient diagnosis and indications, so there were no interobserver variances. In the patient records, it was remarkable that hardly any of these patients were under medical supervision by an internist or a nephrologist. This may be because all our patients described were referred by general practitioners to the vascular surgeon. Our patients, therefore, may well be representative for those who are referred for angiography for evaluation for PVD. However, it may not be representative for the whole PVD population, because it is known that many patients with PVD go unrecognized in general practice (35).

Conclusion

Incidental RAS is a frequent finding in patients who are evaluated for PVD by DSA, and this finding predicts mortality independent of other risk factors. Therefore, risk assessment in patients who undergo angiography for PVD could be improved by consideration of the renal arteries. Future prospective studies should examine whether RAS is a marker or mediator of poor prognosis and whether prognosis can be improved by specific intervention or medical therapy.

Acknowledgments

We thank Dr. C.A. Stegeman for expert help data analysis and R. Balena for the data collection.

References

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